PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
PHM.70580/WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/03139	15/08/2000	21/08/1999
Applicant		
ASTRAZENECA AB		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   IMIDAZO'1,2-A!PYRIDINE AND PYRAZOLO'2,3-A!PYRIDINE DERIVATIVES

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PHM.70580/WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/03139	15/08/2000	21/08/1999
International Patent Classification (IPC) or national classification and IPC C07D471/04		
Applicant ASTRAZENECA AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05/03/2001	02.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Wörth, C Telephone No. +49 89 2399 8726

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/03139

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-72 as originally filed

Claims, No.:

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12
Industrial applicability (IA)	Yes:	Claims	1-12
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. Reference is made to the following documents:

D1: US-A-5 521 184 (ZIMMERMANN JUERG) 28 May 1996 (1996-05-28)
D2: WO 96 40143 A (SMITHKLINE BEECHAM CORP) 19 December 1996 (1996-12-19)

2. Section V: Reasoned statement under Article 35(2) PCT with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The present international application discloses pyrimidine compounds of general formula (I) as inhibitors of cell cycle kinases showing selectivity for CDK2, CDK4 and CDK6. The compounds are disclosed to possess anti-cell-proliferation properties.

2.1 Novelty

Document D1 discloses in general formula (I) N-phenyl-2-pyrimidine-amine derivatives. In view of the definitions of R_1 or R_2 in D1, the subject-matter of the present international application differs in the definition of substituent **"A"** at position 4 of the pyrimidine-core from document D1.
Document D2 discloses 1,4,5-substituted imidazole compounds. Although R_1 or R_2 are inter alia defined as 4-pyrimidine (see page 17, line 10-13), there is no indication that the imidazol-moiety can form a fused system according the definitions given for "A" in the present international application. Furthermore, the nitrogens of **"A"** in the present application are not substituted in view of the definition of R_2.

Accordingly, the subject-matter of claims 1-12 fulfills the requirements of Art. 33(2) PCT.

2.2 Inventive step

Document D1 discloses N-phenyl-2-pyrimidine-amine derivatives as compounds exhibiting anti-tumoral and anti-arteriosclerotic properties (see col. 4, line 1-3). In particular, an inhibitory effect on certain cyclines, involved in the regulation of certain phases of cell division, is described on col. 8, line 19-39.

Accordingly, document D1 is at present considered as relevant prior art. It is pointed out, that D1 defines the substituent R_1 inter alia as 1H-indolyl, whereas this substituent is bound to the pyrimidine-core via one of its five-membered ring carbon atom. In particular, example 33 **N-(3-(1,1,2,2-tetrafluoroethoxy)phenyl)-4-(3-indolyl)-2-pyrimidine-amine** is considered as the most pertinent compound.

In view of this document, the problem to be solved by the present application can be considered as the provision of pyrimidine compounds exhibiting the same qualitative activity as D1.

The solution to the problem consists merely in a replacement of a bridging carbon atom of the indolyl-substituent of D1 by a bridging nitrogen atom.

With regard to the technical teaching of document D1, col. 1, line 25 - 33, disclosing multiple nitrogen containing ring systems as suitable substituents of pyrimidine in order to obtain cycline selective properties, **this solution has to be considered as obvious**. The replacement of a bridging carbon atom of the indolyl- substituent of D1 by a bridging nitrogen atom is according to the technical teaching of D1, col. 1, line 25 - 33 defining R_1 considered as a minor bioisosteric modification.
Moreover, underlying the principles of structure-activity relationship (SAR), it is stressed that similar qualitative biological activity for structurally similar compounds can be expected. As a consequence thereof, SAR allows the prediction that for formal analogisations the pharmaceutical activity will be maintained.

Consequently, the further problem to be solved can be regarded as the provision of pyrimidine derivatives with unexpected effects. In this context it is noted, that SAR does not allow the prediction as to whether the quantitative biological activity for structurally similar compounds is better or worse. As a consequence thereof, an unexpected effect (e.g. improved antiproliferative activity) can be considered as an indication for inventive step. However, the Applicant has not shown, that the claimed compounds are likely to have such an unexpected effect compared to those described in the prior art, in particular the nearest possible compounds, which apparently are represented by the compounds exemplified in D1, in particular in example 33 of D1.

As far as the scope of the claims is concerned, the Applicant's attention is drawn to the point, that only such compounds can be claimed which represent a solution of the problem underlying the application in suit. The extent of a reasonable generalisation depends on the credibility that substantially all the alternatives claimed must be a solution to the problem. Extremely broad generalisations like e.g. the definition of

R^1 = from halo to optionally substituted N,N-(C_1-C_3alkyl)$_2$sulphonamyl with n = 0-2, **whereas only bromo (ex. 80-82) and hyroxyethylthio (ex. 91)** has been exemplified or

R^2 = from halo to optionally substituted heterocycle (see also definitions of G and Q) **whereas only methyl (ex. 1-5), thien-2-ylthio (ex. 87) and dimethylaminoethylthio (ex. 88)** has been exemplified and

R_4= A-E- wherein A is from C_1-C_6alkyl to optionally substituted heterocyclic group and E is from direct bond to -N(R_a)SO_2- wherein R_a is optionally D-substituted alkyl, wherein D is from halo to optionally K-substituted N,N-(C_1-C_6alkyl)$_2$sulphonamyl, wherein K is from halo to N-methyl-N-ethylsulfonamyl

embracing even other pharmacophores are in contradiction to the basis of qualitative structure-activity-relationships. Taking into account the relevant state of the art and the common knowledge, it appears to be not predictable, that all alternatives would achieve the technical effect.

Furthermore, the expression "optionally substituted" found throughout the claims embraces an unlimited number of possibilities which inherently will not lead to compounds solving the given problem, that is to say, having cycline specific activity.

Accordingly, the present application does not meet the requirements of Art. 33(3) PCT.

3. Section VIII: Certain observations on the international application

3.1 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.

3.2 Claim 8 apparently comprises all the features of claim 7 and is therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).

WO 01/14375
PCT/GB00/03139

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
BRYANT, Tracey
AstraZeneca
Global Intellectual Property
Box 272
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG
ROYAUME-UNI

CODE	P.O. DATE	NTD

REC'D 09 MAR 2001 GIPS

DATA ENTERED

FINAL CHECK

IMPORTANT NOTICE

Date of mailing (day/month/year)	
01 March 2001 (01.03.01)	
Applicant's or agent's file reference	
PHM.70580/WO	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/GB00/03139	15 August 2000 (15.08.00)	21 August 1999 (21.08.99)

Applicant
ASTRAZENECA AB et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AG,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,DZ,EA,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   01 March 2001 (01.03.01) under No. WO 01/14375

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

Continuation of Form PCT/IB/30[illegible]

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

Date of mailing (day/month/year)	IMPORTANT NOTICE
01 March 2001 (01.03.01)	
Applicant's or agent's file reference	**International application No.**
PHM.70580/WO	PCT/GB00/03139

The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

PATENT COOPERATION TREATY

LCP

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

CODE	DATE	NTD
ANKOM 09 NOV 2001		GIPS
DATA ENTERED		
FINAL CHECK		

9 NOV 2001

To:

BRYANT, Tracey et al
ASTRAZENECA
Global Intellectual Property
P.O.Box 272
Mereside, Alderley Park
Macclesfield, Cheshire, SK10 4GR
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	02.11.2001
Applicant's or agent's file reference: PHM.70580/WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/03139	15/08/2000	21/08/1999

Applicant: ASTRAZENECA AB et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer
Ferro Vasconcelos, M

Tel.+49 89 2399-~~7365~~ 7271